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Epidemiology of Gastrointestinal Cancer

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Some 99,000 new cases of cancer of the colon are expected next year, an incidence rate higher than that for both cancer of the lung and cancer of the breast. Evidence from geographic pathology suggests that some environmental factors play a strong role in its etiology. Data obtained in the 1959 survey of one million people by the American Cancer Society and followed since, has failed to show correlation with any of the large number of factors listed. It is suggested that the etiology is one of multiple factors. The synergistic effect of exposure to asbestos and cigarette smoking in the production of bronchogenic carcinoma is demonstrated by data on cohorts of insulation workers. There was also a modest increase in the number of deaths from gastrointestinal cancer in asbestos workers, but smoking did not seem to act in synergistic fashion at that site, except perhaps in the esophagus. Deaths from cancer occurred almost entirely after a period of 20 years or more from initial exposure. The death rate from cancer tended to increase with duration of exposure, but a distinct rise over the expected was seen in those who had been exposed less than one year to amosite dust.

Epidemiological studies can be used for a variety of purposes. Probably the most important is to identify factors of significance in the etiology of specific disease. Studies with this aim fall into two categories, generally called hypothesis seeking and hypothesis testing. I think it fair to say that, up to this point, most epidemiological studies associated with cancer of the large bowel have been hypothesis seeking. We have not had many good hypotheses to test.

It may be of interest to review the relative importance of cancer of the colon and rectum compared to other tumors in the United States projected for 1974. Judged in terms of incidence, we expect next year *(1)* some 99,000 new cases of cancer of the colon. This compares with 88,000 projected cases of cancer of the lung and some 90,000 cases of cancer of the breast. In terms of mortality, cancer of the lung is more important, We expect some 75,000 deaths from lung cancer in 1974, some 33,000 deaths from breast cancer, and some 48,000 from cancer of the colon. For comparison I should say that we expect some 20,000 cases of cancer of the pancreas, and about the same number of cases of leukemia. The number of deaths from these two causes will be slightly less.

Of equal interest is the fact that, when we compare age-standardized death rates for cancer of the colon in various countries, they are not the same. For example, the elegant studies of Segei *(2)* showed that Scotland, Denmark, Canada and New Zealand were at the top of the list, with around 20 deaths per 100,000 of age-standardized population. At the bottom of the list were Chile, Finland, Japan, and Israel, with something between 5 and 10 per 100,000 of population. These rates are significantly different.

In the United States, our white population fell somewhere in between and our nonwhite population at a somewhat lower level. The time trends, when looked at from 1950 to the present time, seem to indicate that the highs and the lows are coming together, with England, Scotland and Wales declining and with Chile and Japan going up.

Another interesting set of data has been made available in the studies of Haenzel and others *(3)*, in which they have shown that the cancer rates for those who migrate from country A to

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country B tend to change after migration to those that exist in country B. Moreover, their children tend to have the rates of the country to which their parents migrated. This has been seen, for example, in the stomach cancer rates of Japanese who, after migration to the United States tend to have lower rates; and their children born in the United States have still lower rates *(3)*. This strongly suggests that there is some exposure factor which is more prevalent in Japan than in the United States. The reverse situation obtains for cancer of the colon, and this may be an important factor in its etiology. There may be some dietary factor or some particular component of the diet that is responsible. Haenzel *(3)* and Berg *(4)* have both suggested that meat may be a factor. Others have considered that fat and cholesterol may be responsible *(5)*. Burkett *(6)*, on the basis of his studies in Africa, has suggested that intestinal stasis, the bulk of the stool and the consistency of the stools probably play a role.

We have looked at this in another way. In 1959 the American Cancer Society, under the direction of E. Cuyler Hammond, enrolled one million people in a prospective study in the United States. Some 200-odd questions were asked—where you were born, how old you are, whether you drink milk, whether you ever had tuberculosis, whether you eat fried foods, whether you smoke and if you smoke how old you were when you began, and so forth. All of these data were stored on computer tapes, and since that time Hammond has been following these million people with the assistance of some 68,000 volunteers of the American Cancer Society. All deaths are recorded and the data analyzsed to see whether any of the factors recorded in 1959 have a relationship to the death rates since then *(7)*.

For our purposes today it may be of interest to look at the correlations with death rates for cancer of the colon and rectum. I can summarize the results by saying that they have been meager. High and low values for potatoes, candies, pancakes, cooked vegetables, meat and poultry, cheese, fruits, butter, fish, green salads, eggs; such characteristics as relative weight, exercise habits, religious groups, population densities, urban versus rural dwelling, hours of sleep, cigarette smoking, nervous tension, education, etc.; none of them even suggest a hypothesis worthy of further investigation.

To summarize to this point, in our studies and looking at what has been evaluated elsewhere, we have found no single factor to be of significance despite rather strenous attempts. On the basis of these experiences you can come to one of two hypotheses. Either, that there are many as yet unidentified factors, each of which acting alone is capable of producing the disease; or, that there are critical combinations of several different factors, probably including diet, heredity, and environmental agents, which are responsible for the occurrence of the disease. Hammond and I lean toward the second of these hypotheses; that multiple factors are involved.

Multiple factor etiology of cancer has been demonstrated in many experimental studies and experimental models, such as the development of mammary cancer in mice. I would like to review another example of multiple factor etiology which has been demonstrated in man. Table 1 gives the mortality data of a group of insulation workers in the New York Metropolitan area *(8)*. The cohort was composed of 632 asbestos insulation workers who were members of a particular union on January 1, 1943. Hammond and I followed this group until December 31, 1962. Age, year, and sex specific rates indicated that there should have been some 203 deaths among them. They actually had 255. The total mortality was increased, and the reason for the excess mortality lay largely in deaths from intrathoracic cancer, with 6.6 expected but 45 observed. The large majority of the intrathoracic cancers were bronchogenic carcinomas, with a number of pleural mesotheliomas. Interestingly, and this was somewhat unexpected by us, we found that, whereas there should have been 9 or 10 deaths from cancer of the gastrointestinal tract, there actually were 29 — a modest increase. However, this did not seem to be conclusive, owing to the rather small numbers involved and the fact that this was only one cohort.

The survivors in this cohort, when examined on January 1, 1963 were asked about their cigarette smoking habits. Of the 370 individuals examined, 87 had never smoked cigarettes; but there were 283 who had a history of regular cigarette smoking. This group of survivors was continued under observation until April, 1967, and we looked at the lung cancer deaths. Of the 87 individuals who had never smoked cigarettes, less than 1 death would have been expected according to the American Cancer Society's smoking specific rates *(9)*; actually there were none

Table 1. Observed and expected number of deaths among 632 asbestos workers exposed to asbestos dust 20 years or longer (1943–1962).

	Deaths				
	1943–1947	1948–1952	1953–1957	1958–1962	Total, 1943–1962
Total, all causes					
Observed (asbestos workers)	28	54	85	88	255
Expected (U.S. white males)	39.7	50.8	56.6	54.4	203.5
Total cancer, all sites					
Observed (asbestos workers)	13	17	26	39	95
Expected (U.S. white males)	5.7	8.1	13.0	9.7	36.5
Cancer of lung and pleura					
Observed (asbestos workers)	6	8	13	18	45
Expected (U.S. white males)	0.8	1.4	2.0	2.4	6.6
Cancer of stomach, colon and rectum					
Observed (asbestos workers)	4	4	7	14	29
Expected (U.S. white males)	2.0	2.5	2.6	2.3	9.4
Cancer of all other sites combined					
Observed (asbestos workers)	3	5	6	7	21
Expected (U.S. white males)	2.9	4.2	8.4	5.0	20.5
Asbestosis					
Observed (asbestos workers)	0	1	4	7	12

(Table 2). Some of these 87 died of asbestosis and at postmortem their lungs had a great deal of asbestos, but none of them died of lung cancer. On the other hand, we would have expected 3 deaths of bronchogenic carcinoma among the 283 with a history of cigarette smoking, and there actually were 24. Asbestos alone did not produce lung cancer, and cigarette smoking should have produced only 3 deaths from lung cancer, but asbestos plus smoking produced many more. This combination exhibits the synergistic effect of multiple causes.

Table 2. Observed and expected bronchogenic carcinoma deaths by smoking habits for 370 asbestos workers. [a]

Smoking habits	No.	Observed deaths	Expected deaths
Never smoked regularly	48	0	0.05
History of pipe, cigar smoking only	39	0	0.13
History of regular cigarette smoking [b]	283	24	2.98
Total		24	3.16

[a] Data of Selikoff *(11)*.
[b] Includes cigarette smokers who also smoked pipe or cigar.

We have continued this group under observation. By December 31, 1971 we had seen only one death from bronchogenic carcinoma among the 87 nonsmokers (and he was a pipe smoker). On the other hand, among the 283 cigarette smokers, there were 41 bronchogenic carcinomas as against an expected 3.3 (Table 3). The experience of this group from 1943 through 1971 indicates that one of every five deaths has been due to bronchogenic carcinoma. Approximately five percent died of mesothelioma, mostly peritoneal. Our experience is the same as that of Smither *(10)* in this regard. About 10% were due to gastrointestinal cancer (Table 4).

These data were inadequate for our purposes in one respect: they included only 87 nonsmokers, and that is not a very large number on which to base strong statements. To investigate this problem further, we established another cohort of insulation workers. On January 1, 1967, there were 17,800 members of this union in the United States and Canada. We undertook a mail questionnaire survey of this group. The answers to the questionnaires gave us a list of 2066 male asbestos workers who had no history of cigarette smoking and 9590 with a history of cigarette smoking (Table 5). In five years we have seen only two cases of lung cancer among the 2066 men with no history of smoking. Asbestos workers who do not smoke cigarettes do not often die of lung cancer. On the other hand, among the 9590 men with a history of smoking, there have been 134 deaths from bronchogenic carcinoma, about five times the expected number. We found no relation between cigarette smoking and death from cancer of the colon and rectum. There was modest increase, but this was not associated with smoking. There

Table 3. Expected and observed deaths among 370 New York-New Jersey asbestos insulation workers, January 1, 1963–December 31, 1971 [a]

	Total		No history of cigarette smoking [b]		History of cigarette smoking	
	Expected	Observed	Expected	Observed	Expected	Observed
Number of men Jan. 1, 1963		370		87		283
Person-years of observation		2520		608		1912
Cancer deaths						
All sites	15.74	94	4.75	15	10.99	79
Lung cancer	4.57	42	1.26	1	3.31	41
Pleural mesothelioma	c	5	c	—	c	5
Peritoneal mesothelioma	c	20	c	7	c	13
Cancer of stomach	0.94	6	0.30	2	0.64	4
Cancer of colon, rectum	2.15	6	0.69	2	1.46	4
Cancer of esophagus	0.37	—	0.11	—	0.26	—
Asbestosis deaths	c	21	c	5	c	16
Deaths from all other causes	69.22	53	22.28	15	46.94	38
Total deaths	84.96	168	27.03	35	57.93	133

[a] Expected deaths based upon age-specific U.S. mortality for white males, disregarding smoking habits. Lung cancer estimates based upon U.S. rates for cancer of lung, pleura, bronchus, and trachea, categories 162 and 163 *(12)*.
[b] Included 39 men who smoked pipe or cigars.
[c] U.S. data not available, but these are rare causes of death in the general population.

Table 4. Expected and observed number of deaths among 623 New York–New Jersey asbestos insulation workers, January 1, 1943–December 31, 1971, 20 yr or more after onset of first exposure to asbestos. [a, b]

	1943–1951		1952–1961		1962–1971		Total 1943–1971	
	Expected	Observed	Expected	Observed	Expected	Observed	Expected	Observed
Cancer deaths								
All sites	11.3	28	18.3	57	17.6	104	47.2	189
Lung	1.5	13	3.5	23	5.1	48	10.1	84
Pleural mesothelioma	c	1	c	2	c	5	c	8
Peritoneal mesothelioma	c	1	c	3	c	20	c	24
Stomach, colon, rectum, esophagus	4.1	7	5.0	18	3.9	16	13.0	41
All other sites	5.7	6	9.8	11	8.6	15	24.1	32
Asbestosis	c	1	c	10	c	22	c	33
All other causes	65.1	44	89.4	94	78.3	61	232.8	199
Total all causes	76.4	73	107.7	161	95.9	187	280.0	421
Person-years of observation:	3726		4406		2898		11030	

[a] 632 members were on the Union's rolls on Jan. 1, 1943. Nine died before reaching 20 years from first employment. All others entered these calculations upon reaching the 20-year from onset of first exposure point.
[b] Expected rates are based upon age-specific death rate data of U.S. National Office of Vital Statistics from 1949–1967. Rates were extrapolated for 1943–1948 from rates for 1949–1955 and for 1968–1971 from rates for 1961–1967.
[c] U.S. death rates not available but these are rare causes of death in the general population.

Table 5. Smoking habits of 17,800 asbestos insulation workers in the United States and Canada, on Jan. 1, 1967.

Age	No. of workers			
	Total	No history of cigarette smoking [a]	History of cigarette smoking	Smoking history not known
<25	1939	281	782	876
25–29	2412	285	1182	945
30–34	2762	314	1435	1013
35–39	2987	309	1640	1038
40–44	2260	223	1395	642
45–49	1589	172	964	453
50–54	1297	134	821	342
55–64	1687	201	965	521
65–74	672	122	314	236
75+	195	25	92	78
Total	17800	2066	9590	6144

[a] Included 609 men who smoked pipes or cigars.

was, however, an increased risk of cancer of the esophagus. There also seemed to be some increased risk of death from asbestosis among the smokers (Table 6).

When studied carefully, the deaths were seen to be almost all more than 20 years from onset of exposure. There were only a limited number of deaths from bronchogenic carcinoma less than 20 years from onset of exposure. The same was true of cancer of the colon and rectum: the increase began to occur more than 20 years after onset of exposure. When we looked at the deaths from pleural mesothelioma, we saw none in less than 10 years, and only a trivial increase in the interval 10 – 14 years from onset of exposure. The increase really began only after 20, 25, 30, 35 years from onset, for both bronchogenic carcinoma and mesothelioma (Table 7).

To determine what duration of exposure is

Table 6. Expected and observed deaths among 17,800 U.S. and Canada asbestos insulation workers, Jan. 1, 1967–Dec. 31, 1971.[a]

	Total		No history of cigarette smoking [b]		History of cigarette smoking		Smoking habits not known	
	Expected	Observed	Expected	Observed	Expected	Observed	Expected	Observed
Number of men Jan. 1, 1967		17,800		2,066		9,590		6,144
Person-years of observation		86,300		10,163		46,615		29,522
Cancer deaths								
All sites	144.09	459	19.92	33	79.58	265	44.59	161
Lung cancer	44.42	213	5.98	2	25.09	134	13.35	77
Pleural mesothelioma	c	26	c	2	c	17	c	7
Peritoneal mesothelioma	c	51	c	9	c	29	c	13
Cancer of stomach	6.62	16	0.95	1	3.60	8	2.07	7
Cancer of colon, rectum	17.51	26	2.52	4	9.53	14	5.46	8
Cancer of esophagus	3.21	13	0.44	0	1.80	7	0.97	6
Asbestosis deaths	c	78	c	4	c	45	c	29
Deaths from all other causes	661.54	555	92.67	36	356.67	286	212.20	233
Total deaths	805.63	1092	112.59	73	436.25	596	256.79	423

[a] Expected deaths based upon age specific U.S. mortality rates for white males, disregarding smoking. Lung cancer estimates based upon U.S. rates for cancer of lung, pleura, bronchus and trachea, categories 162 and 163.
[b] Included 609 men who smoked pipes or cigars.
[c] United States data not available, but these are rare causes of death in the general population.

Table 7. Deaths of lung cancer and pleural mesothelioma among 17,800 asbestos insulation workers in the U.S. and Canada, Jan. 1, 1967–Dec. 31, 1971: relation to elapsed period from onset of work exposure.

Years from onset	No. of deaths: Lung cancer: Expected[a]	Lung cancer: Observed	Lung cancer: Ratio	Pleural mesothelioma (Observed)
<10	0.48	0	—	0
10–14	1.69	4	2.4	0
15–19	4.86	18	3.7	2
20–24	7.55	25	3.3	4
25–29	8.50	41	4.8	7
30–34	6.24	44	7.1	4
35–39	3.53	23	6.5	1
40–44	4.04	24	5.9	3
45–49	3.72	17	4.6	4
50+	3.81	17	4.5	1
Total	44.42	213	4.8	26

[a] Expected deaths are based upon age specific death rate data of the U.S. National Office of Vital Statistics. Rates for 1968—1971 were extrapolated from data for 1961—1967.

Table 8. Distribution by duration of employment of expected and observed deaths of lung cancer among 876 amosite asbestos factory workers, first employed 1941–1945, and observed to Dec. 31, 1971.[a]

Duration of employment	Number of men	Person-years of observation	Deaths of lung cancer: Expected[b]	Deaths of lung cancer: Observed	Deaths of lung cancer: Ratio
<3 months	256	5,869	3.55	13	3.66
3–11 months	294	6,158	3.58	15	4.19
1+ years	326	6,912	4.09	45	11.00
Total	876	18,939	11.22	73	6.51

[a] This table excludes 57 men: 10 died during first year of employment, 39 could not be traced after the first year, 7 had prior occupational exposure to asbestos, and 1 had employment of uncertain duration; 17 men of the 876 were partially traced and remained in the calculations only until lost to observation.

[b] Expected rates are based upon age-specific rate data of U.S. National Office of Vital Statistics, 1949–1967. Rates were extrapolated 1941–1948 from rates for 1949–1955 and for 1968–1971 from rates for 1961–1967.

necessary, we examined the experience of workers at an amosite asbestos products factory. From 1941 to 1945 (the factory closed in 1954) 933 men were employed there. These people had varying durations of exposure; some worked for 1 day, others for the full 13 years. By the end of 1971 we found the same increase in cancers as was seen elsewhere. Where 11 lung cancers were expected, 73 occurred; there was the same modest number of pleural and peritoneal mesotheliomas, the same modest increase of gastrointestinal cancer. The data were then examined for duration of exposure (as distinct from time since onset of exposure), and they fell into three approximately equal groups: worked for less than 3 months; worked 3–11 months; worked for 1 year or more. We found that there was a significant increase in the risk of lung cancer in the group with less than 1 year of exposure, and even in the group with less than 3 month's exposure, although the increase was much greater in the group with more than one year's work (Table 8). The total mortality in these three groups is very much the same, which, considering that the groups were not identical in age, provides an interesting coherence of results.

Finally, as regards tumors other than bronchogenic carcinoma, mesothelioma and gastrointestinal cancer, in 17,800 asbestos workers with 1092 deaths, we found 15 from genitourinary cancer, of which 11 were of the kidney and 4 of the bladder and urethra. It has been stated that lymphomas and leukemias are increased in asbestos workers. We feel that our experience is still too limited to make any statement on this matter. Of all deaths in this cohort, 16 deaths, somewhat over 1%, were due to leukemia and lymphoma. There were 11 deaths from pancreatic carcinoma. More were so listed on the death certificates, but many of them turned out on examination to be peritoneal mesothelioma, gastrointestinal cancer, or metastatic cancer from the lung. About 15 cases, or about 1.5% of all deaths, were due to cancer of the oropharynx of larynx. It is also interesting to note that 11 deaths, or about 1%, were due to cancer or the brain, of which 6 were astrocytomas and the others glioblastomas.

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